THIS OPINION WAS NOT WRITTEN FOR PUBLICATION

Paper No. 54

UNITED STATES PATENT AND TRADEMARK OFFICE

_____

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

_____

Ex parte ROBERT C. ALLEN

_____

Appeal No. 1996-0826
Application No. 08/271,583[1]

_____

ON BRIEF

_____

Before WINTERS, LORIN, and SPIEGEL, *Administrative Patent Judges*.

SPIEGEL, *Administrative Patent Judge*.

DECISION ON APPEAL

This is a decision on appeal under 35 U.S.C. § 134 from the examiner finally rejecting claims 3, 6, 7, 9 through 14, 17, 18, 20, 21, 23, 24, 26, 27, 59 and 61 and refusing to allow claims

[1] Application for patent filed July 7, 1994. According to appellant, this application is continuation of Application 08/137,817, filed October 19, 1993, now abandoned, which is a continuation of 07/660,994, filed February 21, 1991, now abandoned.

1, 5, 8, 15, 19, 22, 25 and 28 as amended subsequent to the final rejection.[2] Claims 28 through 58, the only other claims pending in this application, have been withdrawn from further consideration under 37 C.F.R. § 1.142(b) as not readable on the elected invention. Claim 1 is illustrative:

> 1. A method of selectively inhibiting the growth of pathogenic microbes while not eliminating normal flora in an animal in need of such treatment, comprising the steps of:
>
> a) administering to the animal an amount of a haloperoxidase which is therapeutically effective, in the presence of
>
> i) a peroxide and
>
> ii) bromide or chloride,
>
> wherein said haloperoxidase is selected from the group consisting of myeloperoxidase, eosinophil peroxidase and derivatives thereof,
>
> b) selectively binding said haloperoxidase to the pathogenic microbes,
>
> c) oxidizing the halide and
>
> d) selectively killing the pathogenic microbes while not eliminating the normal flora of the animal.

The references relied on by the examiner are:

Hasegawa et al. (Hasegawa) (published UK patent application)	2,108,387	May 18, 1983

Belding et al. (Belding), "Peroxidase-Mediated Virucidal Systems," 167 *Science* 195-196 (January 9, 1970).

[2]Notwithstanding entry authorization by the examiner (see the advisory action mailed March 1, 1995, Paper No. 40), the amendment filed February 14, 1995, amending claims 1, 5, 8, 15, 19, 22, 25 and 28 and cancelling claims 2 and 16 (Paper No. 39) has not been physically entered in the file record. This clerical processing oversight should be corrected upon return of the above identified application to the jurisdiction of the examiner.

Clark et al. (Clark), "Peroxidase-H_2O_2-Halide System: Cytotoxic Effect on Mammalian Tumor Cells," 45 *Blood* 2, 161-170 (February 1975).[3]

Kanofsky, J., "Singlet Oxygen Production by Lactoperoxidase," 258 *The Journal of Biological Chemistry* 10, 5991-5993 (May 25, 1983).

Klebanoff, S. (Klebanoff (01)), "Myeloperoxidase-Halide-Hydrogen Peroxide Antibacterial System," 95 *Journal of Bacteriology* 2131-2138 (1968).

Klebanoff et al. (Klebanoff (31)), "Toxic Effect of the Peroxidase-Hydrogen Peroxide-Halide Antimicrobial System on *Mycobacterium leprae*," 44 *Infection and Immunity* 2, 534-536 (May 1984).

Lehrer, R., "Antifungal Effects of Peroxidase Systems," 99 *Journal of Bacteriology* 2, 361-365 (August 1969).

The reference relied on by this Merits panel is:

Nedwin et al. (Nedwin)[4] (published European patent application)	361,908	April 4, 1990

[3]At page 3 of the examiner's answer, the examiner lists "Clark et al, Blood, 45(2): 161-170 (1975)" as the "prior art of record relied upon in the rejection of the claims under appeal." It appears that the examiner is relying on the actual article appearing in *Blood*. However, we cannot find the article in this record. Rather, what we find is what appears to be a copy of a printout from an electronic database which contains an abstract of the article. The form PTO-892 attached to the first Office action on the merits mailed February 20, 1992 (Paper No. 8) in the grandparent '994 application cites the article but adds "(Biosis abstract only)." From this we take it that the examiner has only considered the abstract which is contained in the printout. This is unfortunate since obviousness determinations are fact intensive and full text articles are more fact filled than abstracts. We also note that there is no information on the printout establishing when that information relied upon was publicly available on the data base. Consequently, our decision is based on a consideration of the abstract which is contained in the printout.

Upon return of the application, the examiner should clarify the record as to what evidence of obviousness is relied upon in support of the prior art rejections of record.

[4]The Nedwin reference was supplied by appellant in the Information Disclosure Statement filed January 3, 1994 (Paper No. 31).

ISSUES[5]

I. Claims 1-3, 5-15, 17, 19-28 and 59-60 stand rejected under 35 U.S.C. § 103 as being unpatentable over Lehrer, Klebanoff (31) or Belding taken with Kanofsky and Clark and further in view of Hasegawa.

II. Claims 1 and 15 stand rejected under 35 U.S.C. § 103 as being unpatentable over Klebanoff (01) taken with Hasegawa.

We reverse both rejections and institute a new ground of rejection.

In reaching our decision in this appeal, we have given careful consideration to the appellant's specification and claims and to the respective positions articulated by the appellant and the examiner. We make reference to the examiner's answer (Paper No. 46, mailed July 21, 1995) for the examiner's reasoning in support of the rejection and to appellant's substitute brief (Paper No. 45, filed June 16, 1995) for the appellant's arguments thereagainst.

THE INVENTION

Appellant's claimed invention is directed to a method of selectively inhibiting the growth of pathogenic microbes while not eliminating normal flora in an animal. The method comprises a) administering to the animal an amount of a haloperoxidase which is therapeutically effective, in the

[5]According to the advisory action mailed March 1, 1995 (Paper No. 40), the amendment filed February 14, 1995 (Paper No. 39) obviated the final rejection of claims 1, 3, 5-15, 17, 19-28, 59 and 60 under 35 U.S.C. § 112, second paragraph, as indefinite.

presence of a i) a peroxide and ii) a bromide or chloride, b) selectively binding the haloperoxidase to the pathogenic microbes, c) oxidizing the halide and d) selectively killing the pathogenic microbes while not eliminating the normal flora of the animal (substitute brief, page 3).

OPINION

I. The rejection of claims 1-3, 5-15, 17, 19-28 and 59-60 under 35 U.S.C. § 103 over Lehrer, Klebanoff (31) or Belding taken with Kanofsky and Clark and further in view of Hasegawa.

Lehrer discloses that the combination of myeloperoxidase (MPO), iodide and hydrogen peroxide is lethal to several fungal species of *Candida, Saccharomyces, Geotrichum* and *Rhodotorula* fungi as well as to spores of *Asperigillus fumigatus* and *A. niger* fungi (abstract; page 363, col. 2, last para., Table 3). A hydrogen peroxide-generating system could replace hydrogen peroxide in the candidacial system (abstract; page 362, col. 1, first full para. and col. 2, first full para.).

Klebanoff (31) discloses that *Mycobacterium leprae* are killed by the peroxidase-hydrogen peroxide-halide antimicrobial system found in phagocytes (abstract; page 535). The peroxidase is either MPO, released by cytoplasmic granules in neutrophils into the phagosome, or eosinophil peroxidase (EPO), released by eosinophil granules either into the phagosome or extracellularly (page 534, first para.). EPO and, to a lesser degree, MPO bind strongly to the negatively charged surfaces of microorganisms. Thus, the cidal activity of macrophages is potentiated when the macrophages ingest microorganisms with EPO bound to their surfaces (page 534, first para.).

Belding discloses that the components of the peroxidase (MPO or lactoperoxidase)-halide (iodide, bromide or chloride)-hydrogen peroxide system present in mammalian tissues and extracellular fluids have antibacterial, antifungal and antiviral activity (page 195, col. 1; page 196, col. 1, first full para.).

Kanofsky suggests that the singlet oxygen produced by the peroxidase-halide-hydrogen peroxide system is responsible for the antimicrobial and cytotoxic activity of this system (page 5991, col. 1, para. 1). Clark states that the hydrogen peroxide component of the peroxidase-hydrogen peroxide-MPO system could be replaced by a peroxide-generating system, e.g., glucose and glucose oxidase, or by a peroxide-producing bacteria, e.g., pneumococci or streptococci (abstract printout).

The examiner acknowledges that the references fail to disclose the selective nature of the peroxidase-halide-hydrogen peroxide system, but asserts that such selectivity is either an inherent feature of the system or would have been obvious in view of the teachings of Hasegawa (answer, pages 5 and 9). Hasegawa found that a composition comprising MPO and an alkali metal halide in a specific ratio, even in the absence of hydrogen peroxide, can be an effective antimicrobial pharmaceutical composition against microorganisms with diminished or no catalase synthesizing activity (page 1, lines 65-73; page 2, line 104 - page 3, line 11).

Here, all of the claims on appeal require "selectively killing the pathogenic microbes while not eliminating the normal flora of the animal." Although "[a]ppellant's claims utilize the same ingredients (a

peroxidase, halide and peroxide) as the references in order to inhibit the growth of microorganisms" (answer, page 9), that fact alone does not establish that one of ordinary skill in the art would have appreciated or recognized that the combined use of peroxidase, halide and peroxide would have the effect of selectively killing the pathogenic microbes without eliminating the normal flora of a treated animal. Inherency and obviousness are different concepts. *In re Shetty*, 566 F.2d 81, 86, 195 USPQ 753, 756 ("inherency is quite immaterial if ... one of ordinary skill in the art would not appreciate or recognize that inherent result."); *In re Spormann*, 363 F.2d 444, 448, 150 USPQ 449, 452 ("the inherency of an advantage and its obviousness are entirely different questions. That which may be inherent is not necessarily known. Obviousness cannot be predicated on what is unknown."). Furthermore, Hasegawa does not remedy this deficiency.

As noted by appellant, Hasegawa does not disclose or suggest the non-elimination of normal flora from a treated animal (supplemental brief, page 9). The examiner has not pointed out and we do not find where Hasegawa discloses or suggests that a MPO-halide pharmaceutical composition kills only microbes with diminished or deficient catalase activity. Hasegawa only tested catalase-deficient/diminished pathogenic microbes. Thus, not only is the cidal effect of Hasegawa's composition on catalase-positive/normal microorganisms unknown but also there does not appear to be any evidence of record establishing that normal flora comprise catalase-positive microorganisms. At best, Hasegawa in combination with the other references might suggest to one of ordinary skill in the art (a)

that the requisite hydrogen peroxide component of the cidal system could be endogenously supplied, e.g., by the animal's own phagocytes or tissues (Klebanoff (31) and Belding), because Hasegawa observed that a composition comprising MPO

and an alkali metal halide in a specific ratio can be an effective antimicrobial against microorganisms with diminished or no catalase synthesizing activity, *even in the absence of hydrogen peroxide* (page 1, lines 65-73) and (b) that catalase activity might at least partially reduce the cidal activity of the MPO/halide/hydrogen peroxide system by reducing endogenous hydrogen peroxide from the tissue because it is well-known that calatase catalyzes the decomposition of hydrogen peroxide in animal tissue.[6] Moreover, as argued by the appellant, Klebanoff (01) "teaches the killing of *Lactobacillus acidophilus*, which is a component of normal flora in humans (see page 2136...)" by the MPO-halide-hydrogen peroxide antibacterial system (supplemental brief, page 11). This last argument based on Klebanoff (01) has not been rebutted by the examiner.

Accordingly, we find that the examiner has not set forth a factual basis which is sufficient to support a conclusion of *prima facie* obviousness of claims 1-3, 5-15, 17, 19-28 and 59-60 over Lehrer, Klebanoff (31) or Belding taken with Kanofsky and Clark and further in view of Hasegawa.

[6]See the copy of White, Handler and Smith, PRINCIPLES OF BIOCHEMISTRY, page 381 (fourth edition 1968) attached to this decision.

II. *Claims 1 and 15 stand rejected under 35 U.S.C. § 103 as being unpatentable over Klebanoff (01) taken with Hasegawa.*

Klebanoff (01) describes the antibacterial effect of MPO-halide-hydrogen peroxide on *Escherichia coli* and *Lactobacillus acidophilus* (page 2133, col. 1 - page 2134, col. 2). Hasegawa has been discussed *supra*.

The examiner again acknowledges that Klebanoff (01) fails to disclose the selective nature of the peroxidase-halide-hydrogen peroxide system, but asserts that such selectivity is either an inherent feature of the system or would have been obvious in view of the teachings of Hasegawa (answer, pages 7-8).

Accordingly, for the same reasons set forth in the preceding rejection, we find that the examiner has not set forth a factual basis which is sufficient to support a conclusion of *prima facie* obviousness of claims 1 and 15 over Klebanoff (01) taken with Hasegawa.

NEW GROUND OF REJECTION - 37 C.F.R. § 1.196(b)

Anticipation by a prior art reference does not require either the "inventive concept" of the claimed subject matter or the recognition of inherent properties that may be possessed by the prior art reference. *Verdegaal Bros. Inc. v. Union Oil Co.*, 814 F.2d 628, 633, 2 USPQ2d 1051, 1054 (Fed. Cir. 1987), *cert. denied*, 484 U.S. 827 (1987). The law of anticipation only requires that the

claims on appeal "read on" something disclosed in the reference. *Kalman v. Kimberly-Clark Corp.*, 713 F.2d 760, 772, 218 USPQ 781, 789 (Fed. Cir. 1983), *cert. denied*, 465 U.S. 1026 (1984).

Claims 1, 5, 14, 15, 19 and 28 are rejected under 35 U.S.C. § 102 as anticipated by Nedwin.

Nedwin discloses a method for killing target cells, e.g., cancer cells, bacteria, fungi, yeast, protozoa, viruses and other parasites, having a characteristic surface antigen in a subject having such cells, comprising administering *in vivo, ex vivo* or *in vitro* a composition comprising an effective amount of a peroxidase, preferably myeloperoxidase, conjugated to a first binding agent capable of specifically binding to the surface antigen, preferably an antibody (i.e., a myeloperoxidase derivative)[7] and a sufficient amount of a hydrogen peroxide-producing enzyme system conjugated to a second binding agent (which may be identical to the first binding agent) capable of specifically binding to a surface antigen (page 3, lines 10-21 and 49-54). In the presence of hydrogen peroxide, the peroxidase converts local halide ions, particularly iodide and chloride, into cytotoxic halide species (page 4, lines 28-29). The specific binding conjugates “provide an very fast, specific killing action” (page 7, line 6). Selective killing, e.g., cytotoxicity against myeloma cancer cells and lack of toxicity to non-target cells, is demonstrated in the examples on page 8. The antibody-targeted specific killing action of target cells

[7]According to the specification, “[i]llustrative examples of useful derivatives include haloperoxidases which have been conjugated to antibodies, antibody fragments, lectins or other targeting moieties which are capable of specifically recognizing and selectively binding to antigens, receptor sites, or other distinguishing features on the surface of target microbes or target cells, such as cancer cells” (page 15, lines 31-36).

and the lack of toxicity to non-target cells disclosed by Nedwin reads on the claimed selective killing of pathogenic microbes (i.e., target cells) while not eliminating the normal flora (i.e., non-target cells).

CONCLUSION

To summarize, the decision of the examiner (I) to reject claims 1-3, 5-15, 17, 19-28 and 59-60 under 35 U.S.C. § 103 as being unpatentable over Lehrer, Klebanoff (31) or Belding taken with Kanofsky and Clark and further in view of Hasegawa is **reversed** and (II) to reject claims 1 and 15 under 35 U.S.C. § 103 as being unpatentable over Klebanoff (01) taken with Hasegawa **reversed**. However, claims 1, 5, 14, 15, 19 and 28 are rejected under 35 U.S.C. § 102 as anticipated by Nedwin.

TIME PERIOD FOR RESPONSE

This decision contains a new ground of rejection pursuant to 37 C.F.R. § 1.196(b) (amended effective Dec. 1, 1997, by final rule notice, 62 Fed. Reg. 53, 131, 53, 197 (Oct. 10, 1997), 1203 off. Gaz. Pat. & Trademark Office 63, 122 (Oct. 21, 1997)). 37 CFR § 1.196(b) provides that, "A new ground of rejection shall not be considered final for purposes of judicial review."

37 C.F.R. § 1.196(b) also provides that the appellant, WITHIN TWO MONTHS FROM THE DATE OF THE DECISION, must exercise one of the two following options with respect to new ground of rejection to avoid termination of proceedings (§ 1.197(c)) as to the rejected claims:

(1) Submit an appropriate amendment of the claims so rejected or a showing of facts relating to the claims so rejected, or both, and have the matter reconsidered by the examiner, in which event the application will be remanded to the examiner ....

(2) Request that the application be reheard under § 1.197(b) by the Board of Patent Appeals and Interferences upon the same record ...

No time period for taking any subsequent action in connection with this appeal may be extended under 37 CFR § 1.136(a).

REVERSED - 1.196(b)

SHERMAN D. WINTERS Administrative Patent Judge	)
HUBERT C. LORIN Administrative Patent Judge	) BOARD OF PATENT) APPEALS) AND) INTERFERENCES
CAROL A. SPIEGEL Administrative Patent Judge	)

CAS/kis
CHRISTENSEN, O'CONNOR, JOHNSON & KINDNESS, PLLC
1420 FIFTH AVENUE, SUITE 2800
SEATTLE, WA 98101-2347